The Gutsy Side of Bone

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Though surgical removal of the stomach has long been linked to low bone mass, the molecular mechanism has been elusive. Amling and coworkers now demonstrate that gastric cell acid production is necessary for calcium absorption. Mice lacking this acidification develop hypocalcemia, with increased parathyroid hormone and osteoclast differentiation, and decreased bone mass.

For a long time, and for unclear reasons, bone biology was like Rodney Dangerfield—it could not get any respect. The long-held view was that beyond the interesting questions raised during development, the skeleton was after birth a mere conglomerate of calcified, rather inert, tubes whose functions were influenced only by sex steroids and parathyroid hormone (PTH), a hormone promoting osteoclast differentiation and bone resorption. This view contrasted strikingly with a multitude of clinical observations, all suggesting possible functional relationships between the skeleton and the rest of the body. In retrospect, these clinical observations were simply stating the obvious: the skeleton is like any other organ—its integrity depends upon but also affects many other organs. It is only recently, through mouse genetic studies, that bone physiology has become more interesting. In more than one case, this experimental approach has provided a molecular explanation of clinical observations.

For example, since the early part of the 20th century, it has been known that the absence of the stomach, or more generally a major gastrointestinal tract (GI) disturbance, is associated with decreased bone mass and sometimes decreased mineralization of the bone extracellular matrix (Mellström et al., 1993; Melton et al., 1999). This well-established observation has, however, lacked a molecular explanation. In a very elegant study Amling and colleagues have now uncovered a molecular basis for the low bone mass induced by gastrectomy (Schinke et al., 2009). In so doing they provide additional evidence for the physiological importance of the emerging gut-bone axis (Rosen, 2009).

Schinke et al. set out to understand why some forms of osteopetrosis, a high bone mass disease caused by a decrease or absence of bone resorption, also present a decrease in bone mineralization—i.e., rickets (the combination of rickets and osteopetrosis is also termed osteopetrorickets). Rickets can be caused by either a decrease in matrix mineralization by the bone-forming osteoblasts or by an imbalance in calcium homeostasis, for example resulting from GI disturbance.

In a thorough review of previously described osteopetrotic mice models, Schinke et al. found one, the *oc/oc* mouse bearing mutations in the gene *Tcirg1*, with decreased mineralization characterized by defective osteoclast acidification of the extracellular milieu (Li et al., 1999). In contrast, rickets was not observed in another osteopetrotic model, the *Src* −/− mouse, in which acidification may be less affected (Soriano et al., 1991). Wild-type osteoblasts do not express *Tcirg1*, the gene mutated in *oc/oc*. In addition, *oc/oc* osteoblasts mineralized normally in vitro. These data suggested that rickets in *oc/oc* mice were not of osteoblast origin. Consistent with this contention, the authors went on to show that *oc/oc* mice were hypocalcemic, and that their rickets were fully rescued by normalizing their serum calcium levels.

Tcirg1 encodes an osteoblast-specific subunit of the vacuolar ATPase, a proton pump mediating acidification of the extracellular space (Li et al., 1999). Amling and colleagues now show that *Tcirg1* is also

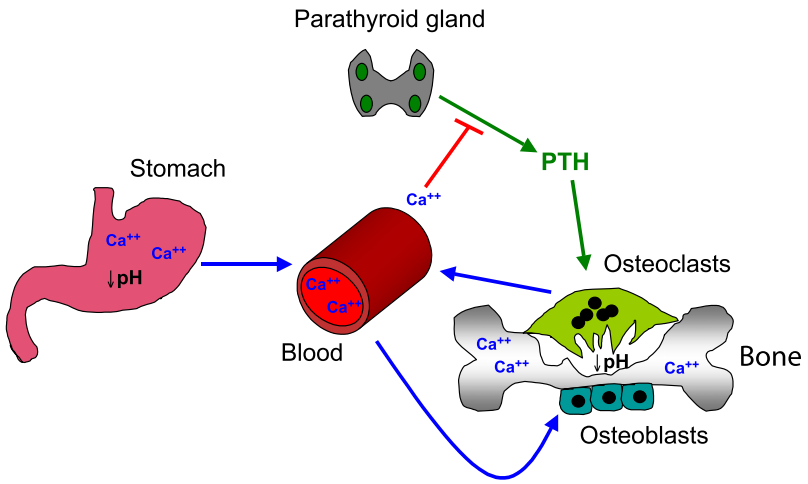

Figure 1. Control of Bone Resorption by the GI Tract
Stomach acidity (↓pH) is required for proper calcium absorption (Ca^{2+} in blue) in the GI tract and is essential to maintain levels of normal serum calcium. Serum calcium in turn negatively regulates parathyroid gland secretion of PTH, a hormone stimulating osteoclast differentiation and bone resorption. Bone resorption also occurs at low pH and contributes to maintaining serum calcium. Calcium is deposited into bone by osteoblasts during bone matrix mineralization. A high stomach pH results in calcium malabsorption and stimulation of PTH secretion, resulting in increased bone resorption. While bone resorption partly maintains serum calcium levels, osteoporosis also results. In osteopetrorickets, both bone resorption and stomach calcium absorption are defective, resulting in hypocalcemia and decreased bone matrix mineralization.

expressed in acid-producing parietal cells of the stomach, both in mice and humans. They next showed that, as one would expect, inactivation of this gene in *oc/oc* mice or in osteopetrotic patients results in defective stomach acidification, a condition that hampers calcium absorption. This low calcium serum concentration in turn increases PTH secretion, which then favors osteoclast differentiation. However, this cannot translate into increased bone resorption since the *oc/oc* osteoclasts are not functional. To further support their hypothesis, they analyzed another mutant mouse strain, *Cckbr* −/− mice that present a hypochlorhydria, a reduction in chloride ion concentration in the stomach, due to a decreased number of parietal cells. These mutant mice also present a mild but significant hypocalcemia, and a slight increase in PTH and in osteoclast numbers. Taken together, these observations suggest that the ability of the stomach to acidify is required for proper calcium absorption. Indeed, the hypocalcemia of the *Cckbr* −/− mice is associated with osteoporosis secondary to an increase in osteoclast activity, and is fully reversible by adding calcium to the diet. The difference in serum calcium levels between *oc/oc* and *Cckbr* −/− mice highlights the importance of calcium release from the bone ECM by osteoclasts, illustrating the role of the skeleton as a reservoir for physiological calcium homeostasis (Figure 1).

The paper by Amling and colleagues is original in illuminating a relationship about which little had been known mechanistically. Relying on elegant genetic, physiological, and histological studies, this work highlights the dependence of bone as a tissue on the GI tract. It is not surprising that the GI tract, a gateway for nutrients, proteins, and minerals, affects and controls of bone mass. Indeed, protein intake affects bone formation and the severity skeletal dysplasia, and serotonin, a duodenum-specific hormone, inhibits bone formation (Elefteriou et al., 2006; Yadav et al., 2008). Taken together, these studies suggest that the complexity and importance of the relationship between the GI tract and the skeleton has yet to be fully described.

REFERENCES

Elefteriou, F., Benson, M.D., Sowa, H., Starbuck, M., Liu, X., Ron, D., Parada, L.F., and Karsenty, G. (2006). Cell Metab. *4*, 441–451.

Li, Y.P., Chen, W., Liang, Y., Li, E., and Stashenko, P. (1999). Nat. Genet. *23*, 447–451.

Mellström, D., Johansson, C., Johnell, O., Lindstedt, G., Lundberg, P.A., Obrant, K., Schöön, I.M., Toss, G., and Ytterberg, B.O. (1993). Calcif. Tissue Int. *53*, 370–377.

Melton, L.J., 3rd, Crowson, C.S., Khosla, S., and O'Fallon, W.M. (1999). Bone *25*, 61–67.

Rosen, C.J. (2009). N. Engl. J. Med. *360*, 957–959.

Schinke, T., Schilling, A.F., Baranowsky, A., Seitz, S., Marshall, R.P., Linn, T., Blaeker, M., Huebner, A.K., Schulz, A., Simon, R., et al. (2009). Nat. Med. *15*, 674–681. Published online on May 17, 2009. 10.1038/nm.1963.

Soriano, P., Montgomery, C., Geske, R., and Bradley, A. (1991). Cell *64*, 693–702.

Yadav, V.K., Ryu, J.H., Suda, N., Tanaka, K.F., Gingrich, J.A., Schütz, G., Glorieux, F.H., Chiang, C.Y., Zajac, J.D., Insogna, K.L., et al. (2008). Cell *135*, 825–837.